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Research Article

FORMULATION AND EVALUATION OF FLOATING BIOADHESIVE TABLETS OF CIPROFLOXACIN HYDROCHLORIDE BYDIRECT COMPRESSION TECHNIQUE

MUKHOPADHYAY S *[1], GOSWAMI L [1], SATHEESH MADHAV NV [2], UPADHYAYA K [3]

[1]Dept of pharmacy, GRD (PG) Institute of management and technology, Dehradun, Uttrakhand, [2]Novel Drug Delivery Research Laboratory, DIT, Faculty of Pharmacy, Dehradun, Uttrakhand, [3]Dept. of Pharmacognosy, Kumaun University, Bhimtal, Uttrakhand.
Email: saan1983.28@rediffmail.com

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ABSTRACT

Ciprofloxacin hydrochloride is mainly absorbed in the proximal areas of the gastrointestinal tract thus the purpose of our study was formulation of floating-bioadhesive tablets to increase the stay period of drug in its absorption area and decrease the dosing interval by increasing the bioavailability. Floating-bioadhesive tablets were prepared by direct compression technique using polymer like hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), carbopol in different ratios. The effervescent base was prepared by using 1:1 ratio of sodium bicarbonate and citric acid. It was observed that tablet with 5% effervescent base shows greater control in drug release in comparison to that of 10%.

Keywords: Ciprofloxacin hydrochloride, Controlled-Release Tablets, Floating, bioadhesive.

INTRODUCTION

Many orally-administered drugs display poor bioavailability when administered as conventional dosage form, i.e., the rate and extent to which the drugs are absorbed is less than desirable. With several drugs, absorption may be as little as 30% or less of the orally administered dose. To compensate for this effect, a very large dose is often administered so that absorption of the therapeutically required quantity of the drug can occur. This technique may prove costly with expensive drugs; and the unabsorbed drug may also have undesirable side effect within the gastrointestinal tract. In addition, poorly absorbed drug often display large inter- and intra subject variability in bioavailability. This problem may be overcome by modified release drug delivery system with prolonged residence time in the stomach[1]. Ciprofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. It is rapidly absorbed orally and shows 60-70% oral bioavailability and 3- 4 hours elimination half-life. Due to its elimination half-life, ciprofloxacin is administered twice to thrice daily [2]. The aim and objective of our current research is to formulate floating and bioadhesive formulations of ciprofloxacin for its controlled delivery to the duodenum which is its best absorption site, thus the oral bioavailability of ciprofloxacin could be improved.

MATERIALS AND METHODS

Ciprofloxacin hydrochloride was supplied as a gift sample from Zydus Cadila, Baghekhola, E.Sikkim, sodium carboxyl methyl cellulose and carbopol was brought from S.D. Fine-Chem. Ltd., Mumbai, hydroxypropyl methyl cellulose from Loba-Chem. Pvt. Ltd., Mumbai and Acrycoat from Thomas Baker Pvt. Ltd., Mumbai. Sodium bicarbonate and citric acid were supplied from Titan Biotech Limited, Rajasthan and S.D. Fine-Chem. Ltd., Mumbai respectively.

Fabrication of bioadhesive floating tablet

All the bioadhesive floating tablets were fabricated by using direct compression technique. In this case all the bioadhesive polymers and the active ingredients were passed through sieve no. 80 individually. Accurately weighed quantity of Ciprofloxacin powder, polymer, effervescent agent and excipients were thoroughly mixed in a glass mortar-pestle [3] and with help of automatic punching machine (Rimek Mini Press-I) by using 12mm flat punch and 3-4 kg/cm^2 pressure, tablet were prepared of desired shape, size and hardness. Formulation compositions of different batches were shown in Table 1.

Determination of floating capacity

Three individual tablets from each formulation were put in an individual flask containing 400ml of 0.1(N) HCL solutions. Then note time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated [4].

Determination of the density of the tablet

The apparent densities of the tablets were calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets were calculated from their height h and radius r (both determined with a micrometer gauge) using the mathematical equation for a cylinder ($V = \pi \times r^2 \times h$) [5].

Determination of drug content in tablets

Three tablets from each batch were selected randomly and transferred to a 100ml volumetric flask filled up with 0.1(N) HCl. Kept it for 48hours then took 1ml from each of volumetric flask and was transferred to the test tubes. Samples were then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength [6].

Measurement of bioadhesive strength of the floating formulation

The force required to separate the sample disk from a model substrate were measured using a modified balance method as reported by Parodi et al. (1996). The formulation was fixed to the base and come into contact with mucosal membrane of sheep tongue; the tablets were left for 5 minute for hydrate. A beaker was placed on a moving platform. The beaker was then slowly raised until the substrate came in the contact with the formulation. A preload of 50g was placed into the stopper for 6min so that the adhesion bonding could be established. After this time, the preload was removed and was added at a constant rate. The addition was stopped as soon as the detachment of the two surfaces was obtained [7].

Determination *of In – Vitro* Dissolution Study

Dissolution study was carried out in USP–II type dissolution apparatus (paddle type). Dissolution study was performed at 50 rpm in 900ml 0.1(N) HCl. 5ml of sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium. The absorption of withdrawn sample was measured

spectrophotometrically with suitable dilution and the corresponding concentration was determined from the respective calibration curve.

Table 1: Ingredient of floating-bioadhesive tablets of ciprofloxacin

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6
Ciprofloxacin hydrochloride	250	250	250	250	250	250
HPMC K4M*	200	225	-	200	176	110
SCMC*	-	-	-	-	44	-
Carbopol-934	-	-	220	200	-	110
Sodium bicarbonate	25	13	13	25	13	13
Citric acid	25	12	12	25	12	12
Talc	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2

* HPMC- Hydroxypropyl methylcellulose; *SCMC- Sodium carboxy methylcellulose

Table 2: Physical properties of floating- bioadhesive tablets of ciprofloxacin

Code	Hardness (kg/cm^2) N=5	Thickness (cm) N=10	Weight variation N=10	Floating lag time (min)	Floating duration (hrs)	Density (g/cm^3) ~ 1 g/cm^3	Drug Content (%)
F_1	4 ± 0.12	0.3 ± 0.12	2.4 ± 1.40	2 ± 0.19	10 ± 1.0	1.002±0.01	95.3±2.8
F_2	4 ± 0.56	0.3 ± 0.19	1.3 ± 1.02	6 ± 0.89	15 ± 1.3	1.056±0.1	98.9±1.3
F_3	3.8 ± 0.21	0.3 ± 0.21	2.4 ± 1.27	4 ± 0.24	18 ± 1.2	1.007±0.09	98.1±1.2
F_4	3.7 ± 0.75	0.3 ± 0.15	1.4 ± 1.36	1.5± 0.15	10 ± 2.8	1.056±0.1	95.2±1.4
F_5	4 ± 0.15	0.3 ± 0.14	4.2 ± 1.17	4.5± 0.25	18 ± 2.1	1.021±0.03	97.2±0.8
F_6	4 ± 0.17	0.35± 0.12	1.7 ± 0.95	5.5± 0.28	21 ± 1.0	1.011±0.06	98.8±1.1

Table 3: Result of correlation coefficients of release data by curve fitting method on zero-order, first-order and Higuchi kinetic model and their diffusion exponent (n)*

Formulation code	correlation coefficients (r^2)			*N*
	Zero-order	First-order	Higuchi	
F_1	0.957	0.972	0.975	0.745
F_2	0.987	0.905	0.972	0.674
F_3	0.976	0.955	0.966	0.679
F_4	0.981	0.950	0.962	0.856
F_5	0.961	0.936	0.985	0.552
F_6	0.989	0.989	0.993	0.688

* $Mt/M\infty = kt^n$

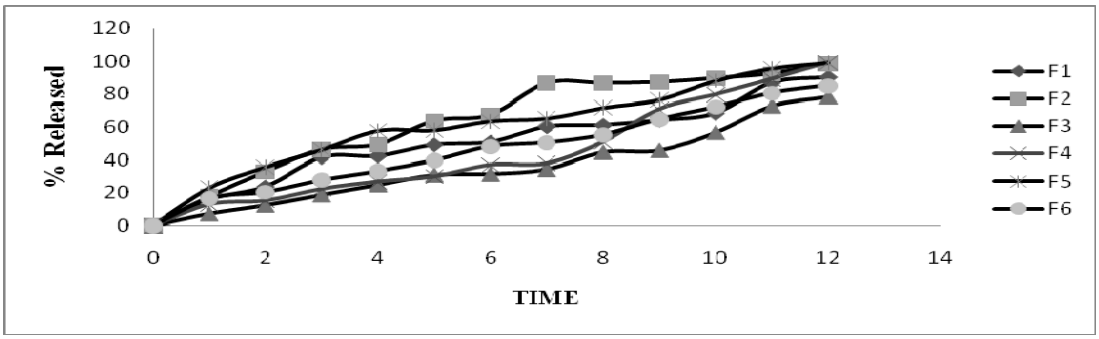

Fig.1: Comparative Zero order release profile of different formulations of floating- bioadhesive tablets of ciprofloxacin

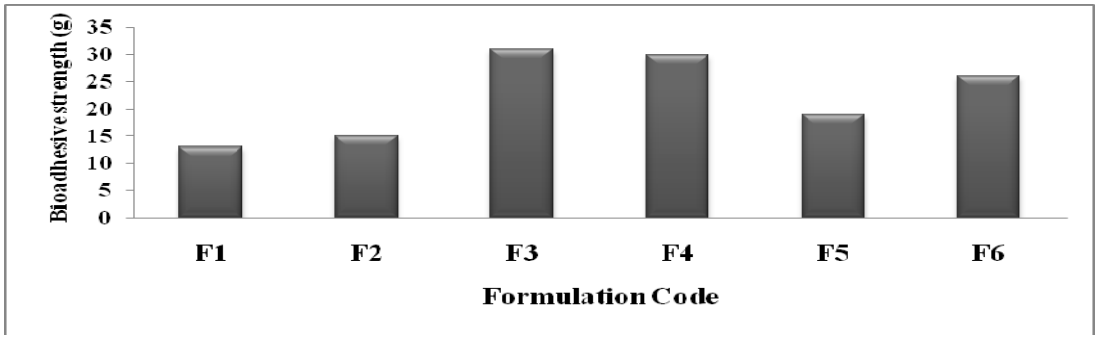

Fig.2: Bioadhesion strength of floating- bioadhesive tablets of ciprofloxacin measured by Modified Balance Method

RESULTS AND DISCUSSION

Floating-bioadhesive tablets of ciprofloxacin hydrochloride were mainly prepared by using different polymer like HPMC-K4M, SCMC and Cabopol-934 either alone or in combination. Effervescent base of tablets were prepared by sodium bicarbonate and citric acid in combination. The tablets were fabricated using direct compression technique. The formulated tablets were subjected for various evaluation parameters like hardness, thickness, density, weight variation drug content and floating capability. Our experimental results (Table 2) revealed that all the formulated tablets were of good quality with regard to hardness (3.7 - 4 kg/cm^2), thickness (0.3 – 0.35 cm), density (~ 1 g/cm^3), weight variation (1.3- 4.2) and drug content (> 90%). As the result of floating capability study showed (Table 2) increasing the effervescent base of tablets from 5% to 10% significantly lower the lag time of floating (From about 6 min to 1.5 min) as well as floating duration (From about 21 hrs to 10 hrs). *In-vitro* drug release showed (Fig. 1) that all formulation released 80% of the ciprofloxacin hydrochloride in 12 hrs study period. Kinetic models describe drug release from immediate and modified release dosage forms [8]. From the result (Table 3) obtained it was observed that the formulations shows value of r^2 over 0.9 for Zero order, Higuchi and First order kinetic model. To predict the mechanism of diffusional release, equation $M_t / M_\infty = kt^n$ was used [9]. Considering the *n* values calculated for the studied tablets (Table 3), in all cases a non-Fickian mechanism is dominant. Applying ANOVA (using Statplus 2007) to the formulations, it was found that all the formulations were statistically significant ($p \leq 0.05$). The otherwise-excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high; however, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded [10]. This serious limitation can be overcome by using bioadhesive polymers to enable it to adhere to the mucous lining of the stomach wall [11]. Bioadhesive strength was measured by modified balance method as reported by Parodi et al. for the prepared formulations. The result of the bioadhesion test (Fig. 2) shows that all the formulations poses good bioadhesive strength.

CONCLUSION

On the basis of present study it was concluded that floating-bioadhesive tablets of ciprofloxacin hydrochloride can increase the gastric residence time as well as bioavailability and thus better patient compliance can be achieved.

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